Effectiveness of altering serum cholesterol levels without drugs

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Drug therapy with statins and other agents can result in dramatic lipid-lowering effects. Despite the wealth of data supporting the beneficial effects of pharmacologic therapy on cardiovascular risk, patients often express a desire to accomplish similar goals with diet alone. And, except for patients with extreme cholesterol elevations, consensus panels all promote dietary therapy as an initial step in the treatment of hyperlipidemia. This review examines a variety of dietary strategies designed to lower lipid levels, including the American Heart Association diet, the Ornish diet, the Mediterranean diet, exercise, phytosterols, fiber, soy products, and fish oil. Though the declines in low-density lipoprotein cholesterol levels with these methods range from 0% to 37%, cardiovascular risk may be more significantly impacted than would be predicted from these changes alone. Significant benefits can be reaped from nonpharmacologic measures.

Despite all of the positive research and trial data about statins and other pharmacologic interventions for treating elevated cholesterol, patients do not take these drugs. In my practice, patients, even those with very high lipids and known heart disease, ask if they could try to lower their cholesterol with diet alone. Or, if they have already started a statin, they want to stop it because of side effects or cost. Drug companies note that upwards of 30% of patients initiated on statins do not continue their prescriptions. These reasons warrant a review of the efficacy of dietary and nonpharmacologic measures to lower cholesterol compared with pharmacologic therapy.

DIET

Unfortunately, even the strict very low saturated fat, low-cholesterol American Heart Association Step 2 diet (see *Table*) only minimally lowers serum cholesterol. Hunninghake et al found a mean 5% reduction in low-density lipoprotein (LDL) cholesterol in patients following this program and discouragingly found an equivalent 6% fall in high-density lipoprotein (HDL) cholesterol, so that ratios were unchanged (1). Low-fat diets as commonly prescribed rarely produce significant LDL declines. Studies performed on controlled metabolic units where intakes are rigidly enforced can demonstrate cholesterol reductions of 15% with diet alone; however, in the real world, people can rarely replicate these results (2).

One exception to this, however, is the Dean Ornish–style diet, which was studied in the Lifestyle Heart Trial (3). This vegetarian diet consists of fruits, vegetables, soybean products, nonfat milk, and yogurt with no oils or animal products *(Table)*. Roughly 7% of calories are from fat, 15% to 20% from protein, and the remainder from complex carbohydrates. Only 12 mg of cholesterol per day is allowed. This prohibition of oils, including olive and canola oil, contrasts with other low-fat diets. Ornish believes that all oils are fundamentally unhealthy as they contain both saturated and unsaturated fats in addition to many calories.

On average, Ornish's patients lost 24 lbs in a year and had a 37% reduction in LDL cholesterol levels (HDL cholesterol levels were unchanged). What is most provocative about this diet/lifestyle program is that there was a 91% reduction in angina frequency and a significant degree of angiographically measured coronary stenosis regression. It is unclear to what degree other lifestyle modifications such as exercise and stress reduction, which are integral parts of the Ornish program, play in these results. Based upon these favorable findings, the National Institutes of Health is embarking upon a multimillion-dollar study of the Ornish diet vs bypass surgery in patients with coronary disease.

The problem with the Ornish diet is it is so stringent that most Americans find adhering to it nearly impossible. In addition, critics of this study note that it had only 48 subjects; thus, the outcome should be viewed skeptically until larger trials are completed. The greatest scientific objection to the Ornish-style diet is that it is now known that high-carbohydrate, low-fat diets raise triglyceride levels, lower HDL levels, and may convert LDL lipoproteins into smaller, denser, and more atherogenic particles (4). Nevertheless, the Ornish diet provides the greatest absolute LDL reduction available by diet alone and is of a magnitude similar to that of high-dose statin therapy, which can reduce cholesterol by 25% to 60% depending upon the drug dose (5).

More widely studied and perhaps more practical for the treatment of patients with coronary artery disease is the Mediterranean diet *(Table)*. In the 1950s, Ancel Keys began studying the dietary habits of 1770 inhabitants of various countries and correlating them with subsequent mortality (6). His landmark study found that the mortality rates from heart disease were 2 to 3 times lower in the countries bordering the Mediterranean Sea compared with Northern Europe and the USA. Keys correlated the findings with the intake of saturated fat, a relationship that has

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Table. Composition of the various diets

	AHA Step 1	AHA Step 2	Ornish	Mediterranean*
Total fat	<30%	<30%	7%	30%
Saturated fat	8%–10%	<7%		8.3%
Polyunsaturated fat	≤10%	≤10%		5%
Monounsaturated fat	≤15%	≤15%		13%
Monounsaturated/ saturated fat ratio	>1.0	>1.0	>1.0	<0.8
Carbohydrates	55%	55%	70%–75%	48%
Protein	~15%	~15%	15%–20%	17%
Cholesterol	<300 mg/d	<200 mg/d	12 mg/d	217 mg/d
Alcohol	0	0	0	5%

*As defined by the Lyon Investigators (9), the general principles of the Mediterranean diet are more bread; more vegetables and legumes; more fish; less meat, with beef, lamb, and pork replaced by poultry; no days without fruit; and no butter or cream. The oils permitted were canola and olive oil exclusively along with a special canola oil–based margarine. Alcohol intake, especially red wine, was allowed and recommended at meals. Four or less eggs per week were allowed.

AHA indicates American Heart Association.

remained valid at a 25-year follow-up. Of the separate Mediterranean cohorts studied, a population from the island of Crete had a strikingly low cardiac mortality, just 2% that of Northern Europe and 5% that of other Mediterranean countries. It was estimated that this Cretan population had the greatest life expectancy of any group in the Western world (7). From the 1950s to the 1970s, Keys examined and wrote extensively about the composition of what he called a "good Mediterranean diet" and, as a result of his research, devised formulas predictive of serum cholesterol levels based upon dietary fat intake (8). Nevertheless, this diet has not been widely embraced in the cardiology community.

Recently, researchers in Lyon, France, prospectively studied the effects of the Cretan Mediterranean diet on a group of 605 postmyocardial infarction patients (9). Patients were randomized either to the Cretan diet or to a "prudent" diet similar in composition to the American Heart Association Step 1 diet (control group). All other aspects of the patients' health care were identical. An astonishing 70% reduction in the incidence of subsequent death and nonfatal myocardial infarction was reported in patients on the Mediterranean diet after a mean follow-up of 27 months, a ratio that was maintained through a final 48-month mean follow-up (10). Even more remarkable is that this mortality benefit occurred despite no difference between the study and the control populations in follow-up LDL and HDL cholesterol levels and only a very modest 6% drop in total cholesterol levels in both groups from 250 mg/dL to 237 mg/dL. The magnitude of benefit reported with the diet alone should be contrasted with that achievable by other routine secondary prevention therapies, including statin drugs (35% event reduction) (11), beta-blockers (15% reduction), and angiotensin-converting enzyme inhibitors (20% reduction) (12).

A number of hypotheses have been advanced to explain how this diet provides benefit independent of its effect on cholesterol levels. One early theory that attributed the longevity benefit to living a relaxed lifestyle on an idyllic Greek island is refuted by the trial being conducted in metropolitan France. Another potential mechanism is that a diet rich in fruits and legumes provides folic acid, which may reduce cardiac risk by lowering plasma homocysteine (13). Also, moderate alcohol consumption is associated with decreased cardiovascular risk in part by increasing HDL levels (14), and both red wine and some Mediterranean plant foods contain large amounts of flavenoids, which are natural antioxidant and antithrombotic substances (15). But the most provocative explanation, advanced by the principal investigators, is that the "prudent" diet contains linoleic acid as an important component whereas the Mediterranean diet contains α-linolenic acid (16). Although both are 18 carbon fatty acids, α-linolenic acid is an omega-3 fatty acid and linoleic is an omega-6 fatty acid. Increased linoleic intake has been shown to promote platelet aggregation and oxidation of LDL. Alternatively, α-linolenic acid has antithrombotic properties and may also be antiarrhythmic (9). α-Linolenic acid is a precursor of other omega-3 fatty acids found in fish and fish oil such as eicosapentaenoic acid (EPA), which may have independent beneficial effects that are discussed later in this review. If, indeed, high intakes of linoleic acid are actually harmful, conformity to the "prudent" diet, as conventionally advocated, may be most imprudent.

The results of the Lyon Heart Study have turned the field of dietary therapy of cholesterol disorders upside down. The time-honored primary goal of diets, namely lowering cholesterol levels, becomes far less relevant than adjusting the composition of the nutritional intake. The beneficial effect of the diet occurs despite seemingly trivial cholesterol reductions. The major difficulty of this new dietary approach for physicians will be the inability to easily measure compliance or success, as specific serum fatty acid levels are not practical to obtain.

EXERCISE

Coupling a low-fat diet with exercise produces better results than diet alone. It is known that exercise can raise the HDL level. Wood et al found that adding regular exercise (approximately 9 miles of walking or jogging per week) to a Step 1 low-fat diet in obese patients produced a 13% increase in HDL cholesterol levels, which offsets the small decline typically seen on a low-fat diet alone (17). This same group expanded these findings to a cohort of nonobese patients with high LDL and low HDL levels. At 1 year, those randomized to a Step 2 diet alone had a 7% to 11% decrease in LDL levels, which was statistically significant. Coupling diet with an exercise program of 10 miles of walking or jogging per week produced a more substantial 14% to 20% decrease in LDL cholesterol levels (18).

Weight loss, in and of itself, has salutary effects on lipid profile. These same investigators, in separate studies of obese patients, found that weight loss, achieved either through diet or exercise, resulted in equivalent increases in HDL cholesterol levels and reductions in triglyceride levels (19). It is especially important to identify and target a subset of patients who have the recently described "insulin resistance syndrome." Typically these patients have central obesity or a relatively large abdomen, glucose intolerance, and hypertension. They have a characteristic lipid pat-

tern with low HDL levels, high triglyceride levels, and smaller, dense LDL particles. In these patients weight loss alone can have a dramatically beneficial effect on lipid profiles (20).

PHYTOSTEROLS

Plants contain a compound very similar in structure to cholesterol. These phyto (or plant) sterols (sitosterol [24-ethylcholesterol] and campesterol [24-methylcholesterol]) occur naturally in small quantities in many plants, such as corn, soybeans, and sunflower seeds. It has been known since the mid-1950s that ingesting large quantities of these sterols decreases cholesterol levels by interfering with absorption of cholesterol. Although these sterols are poorly absorbed by the gastrointestinal tract, they compete effectively with cholesterol for inclusion in mixed micelles, a necessary step for cholesterol absorption. Unable to enter the micelle, cholesterol is unabsorbed and serum levels decline. These plant molecules have been further engineered to make them more potent and palatable. Hydrogenated sitosterol, sitostanol, is itself unabsorbed by the gastrointestinal tract but competes even more effectively for micelles. It can be esterified in canola oil and included in food products such as margarine and salad oil. This is the genesis of the "functional food" product Benecol. Benecol was introduced in Finland in 1995 and is available in the USA as margarine, salad oil, or snack bars. Several large studies have shown that ingestion of 2 to 4 g a day of sitostanol (2 to 3 servings) lowers the total cholesterol by 10% and the LDL level by 14% (21). HDL and triglyceride levels are not altered. Because the sitostanol is completely unabsorbed, no systemic side effects (and specifically no gastrointestinal side effects) are reported. It is estimated that sitostanol reduces cholesterol absorption by 33% to 66%.

Interestingly, most people have elevated cholesterol levels because of increased hepatic lipoprotein synthesis rather than because of hyperabsorption. The former metabolic pathway is what statins target through 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibition. However, a group of patients—perhaps 20% of people—responds poorly to statins; their elevated cholesterol is derived more from hyperabsorption of cholesterol rather than from enhanced hepatic synthesis (22). These patients do especially well with Benecol. Adding Benecol to the regimens of patients who have inadequate responses to statin drugs has been advanced as a logical strategy to interfere with synthesis as well as absorption.

Theoretically, combining a low-fat diet and exercise program with Benecol would produce additive cholesterol-lowering effects. Assuming one could achieve a 15% LDL cholesterol reduction with a Step 2 diet and exercise and an additional 15% reduction with Benecol, a LDL cholesterol reduction of 30% might be possible—rivaling the results of some statins. We would not expect a benefit of this magnitude to be achieved, however, because the lower the total cholesterol presented in the diet, the less meaningful any reduction in absorption. For example, Benecol is unlikely to add anything to an Ornish diet. Plant sterols from soybeans are available in the margarine "Take Control." It has been compared with Benecol in studies and appears to have similar efficacy.

The public health benefits of plant stanol and sterol use have been underappreciated (23). Incorporated widely into the American diet, these products could produce a 30% reduction in the incidence of coronary disease, as it is known that every 1% reduction in LDL cholesterol decreases the risk of coronary disease by 2% over a lifetime.

As a side note, the use of plant sterols has focused light on an obscure disorder, familial phytosterolemia, an exotic autosomal-recessive disease in which homozygotes have increased absorption of phytosterols, high levels of sitosterol and camposterol, and premature atherosclerosis development. I mention this only to contemplate the fascinating scenario of inadvertently feeding increased plant sterol to susceptible patients. This will join the very short list of diseases from which one can die by being a strict vegetarian (24).

FIBER

Soluble fibers—such as psyllium, oat bran, guar gum, and pectin—have been shown to reduce cholesterol levels in multiple studies, although the mechanism of benefit is debated. Most studies have few subjects and are of short duration but consistently show that the inclusion of 10 to 30 g of soluble fiber in a diet results in an approximately 10% reduction in LDL cholesterol. HDL and triglyceride levels remain unchanged (25). Some investigators feel that the fiber actually binds cholesterol or bile salts in the gut and prevents its absorption, working in a way similar to that of cholestyramine. Other investigators have evidence showing that intake of fiber simply reduces the subsequent ingestion of saturated fat and cholesterol (26). Simply put, filling up with a bowl of cereal decreases that craving for a sausage patty. It should be noted, however, that with 1 serving of Cheerios containing just 1 g of soluble fiber and 1 teaspoon of Metamucil containing 2.3 g of psyllium fiber, it takes a prodigious consumption to equal the desired 10 to 30 g a day, so if you consume the recommended amount, you are definitely "already full."

SOY PRODUCTS

Another dietary variation that can lower cholesterol is the substitution of vegetable protein for animal protein in the diet using soy-based products. Replacing 2 servings of milk with soy milk and 1 serving of meat with tofu will lower cholesterol, LDL, and triglyceride levels (27). The magnitude of benefit is greater the higher one's baseline cholesterol, with an expected 7% to 10% reduction for those with moderate cholesterol elevations (200 to 330 mg/dL) who add 30 g a day of soy product to their diet. The mechanism of benefit is uncertain and may be due to phytoestrogens in the soybean, which exert a salutary effect on lipid profiles similar to that of estrogen.

FISH OIL

The lipid-lowering benefits of eating fish have been well known since epidemiologists noted that Greenland Eskimos had a low coronary mortality compared with Danes. Danes eat a high-fat diet. Eskimos eat a high-fat, high-cholesterol diet but one rich in fish, especially those containing the omega-3 fatty acids EPA and docosahexaenoic acid (DHA). These fatty acids lower plasma very low density lipoproteins (VLDL) and triglyceride concentrations by depressing synthesis of triglycerides in the liver. Also, the normal postprandial hypertriglyceridemia and chylomicronemia are dramatically decreased by ingesting fish oil.

Accordingly, fish oil is especially effective at lowering elevated VLDL and chylomicron levels; HDL is not significantly lowered, and LDL effects are variable and highly individualized. In some patients LDL levels will rise, and in others they will fall. Those with significant VLDL and chylomicron elevations are most benefited by incorporating fish or fish oil into their diets (28).

It is suggested that eating 200 to 300 g per week of fish or shellfish (or 2 to 3 fish meals per week) will produce an Eskimo-like preventive benefit on coronary disease. Those fish especially rich in omega-3 fatty acids are anchovies, herring, mackerel, sardines, and salmon. Concentrated omega-3 fish oils are widely available, and 2 to 3 g a day of a 30% concentrate are recommended for those who won't eat fish. You need to look carefully at the product label, however, because fish oil capsules can contain anywhere from 30% to 85% omega-3 fatty acids. Alternatively, pharmacological effects of fish oil on elevated triglycerides and chylomicrons can be achieved with 6 to 15 g a day of fish oil (or 3 to 5 g a day of omega-3 fatty acids). This requires ingesting 10 to 12 tablets of 30%–fish oil concentrate a day. Reduction in triglyceride and chylomicron levels of 60% to 90% have been reported in patients with elevated VLDL and chylomicron levels (29).

Two large prospective studies have reviewed the benefit of fish oil. The Diet and Reinfarction Trial (DART) randomized 2033 men to either a low-fat diet, a high-fiber diet, or a 200- to 400-g per week fish diet (30). There was a remarkable 29% reduction in all-cause mortality at 2 years in the fish diet group vs the other 2 groups. An even larger 62% reduction in ischemic heart disease death was noted in those patients who chose to take fish oil tablets (900 mg omega-3 per day) rather than eat fish. Fish oil has antithrombotic, antiarrhythmic, and anti-inflammatory properties in addition to lipid-lowering effects, which probably account for these results. This may help explain the beneficial results found in the α-linolenic acid–rich Mediterranean diet, as α-linolenic acid is converted to DHA and EPA in the body. DART, however, had a number of confounding factors in its intricate multifactorial design, and the results are tantalizing but not convincing.

The larger GISSI Prevention Study randomized 11,324 Italians with recent myocardial infarctions to 850 mg of omega-3 fatty acids per day, 300 mg of vitamin E per day, neither, or both (31). In the fish oil group there was a statistically significant 20% reduction in total mortality at 3.5 years and a more striking 45% reduction in sudden death, reinforcing a possible antiarrhythmic property of omega-3 fatty acids. Although this study was not designed to investigate this hypothesis, a large majority of the study subjects appeared to be eating components of a Mediterranean diet at baseline, and the extra fish oil produced additive benefits.

SUMMARY

A number of dietary recommendations for patients with elevated cholesterol levels or coronary artery disease show evidence of benefit. In particular, striking mortality benefits have been reported independently of cholesterol-lowering effects. In terms of practical application both for primary and secondary prevention, the Mediterranean diet is both palatable and affordable and is supported by strong epidemiological and control trial data. Combining a Mediterranean diet with a cholesterol-lowering margarine and emphasizing added fish or fish oil would theoretically further augment this effectiveness.

For patients with proven coronary artery disease, however, a target LDL level of <100 mg/dL is recommended, a goal that will probably be further lowered in the next series of consensus guidelines. The vast majority of these patients will require pharmacologic therapy to achieve these goals. Dietary modifications should not be overlooked, however, as they are likely to provide additive benefits.

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